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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/330,903	GONDA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-64 and 66-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-64 and 66-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A terminal disclaimer over US 5,906,202 was received and entered on 11/19/04.

An amendment was received and entered on 11/4/04.

Claim 57 was canceled and claim 72 was added as requested.

Claims 58-64, and 66-72 are pending and under consideration in this Office Action.

This Action contains new grounds of rejection not necessitated by Applicant's amendment and is therefore NON-FINAL.

Drawings

The drawings stand objected to for the reasons of record in the PTO form 948 mailed on 5/4/04.

Priority

This Application claims priority to application number 08/752,946, filed 11/21/96, now US Patent 5,906,202, issued 5/25/99. However, instant claims 57-64, and 66-71 recite a polynucleotide and a condensing agent and there is no support for this limitation in US Patent 5,906,202. Furthermore, '202 provides no support for a lipid-based carrier (instant claims 61 and 62). For these reasons, the priority date for the instant claims is considered to be that of provisional application 60/089,146 which is 6/12/98.

At page 4 of the response, Applicant asserts that they are entitled to claim priority to the disclosure of the '202 patent, because it does support part of the instant

application. The Examiner agrees that Applicant has met the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. However, the '202 patent does not support the instant claims, so the priority date of the instant claims is 6/12/98.

Rejections Withdrawn

The rejection of claims 58-64 and 66-71 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment.

The double patenting rejections of record are withdrawn in view of the terminal disclaimer over US 5,906,202 filed on 11/19/04.

Claim Objections

Claim 72 is objected to. The word --and-- should be inserted after "tract;" immediately before the last clause.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 61, 62, and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 61 and 62 depend from claim 72 and recite aerosol particles comprising condensed polynucleotides, wherein the aerosol particles are further comprised of a cationic lipid. Claims 61 and 62 are silent as to any interaction between the cationic lipid and the nucleic acid, and therefore embrace aerosol particles in which the lipids interact with the nucleic acids, and complexes in which they do not interact with the nucleic acids. For example, the claims embrace aerosol particles comprising both electrically neutral nucleic acids/polycations complexes and cationic liposomes that are independent of the DNA/polycation complexes. However, while the specification discloses cationic lipids as agents that can be used to coat nucleic acids (see page 45, lines 23-27), the specification does not contemplate cationic lipids in formulations wherein the lipids do not interact with the nucleic acids. Because there is no support for this embodiment in the specification, the claims contain new matter. It is suggested that claims 61 and 62 should be amended to require that the cationic lipid must be complexed with the nucleic acid.

Enablement

Claims 58-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes of polynucleotides and polycation condensing agents wherein the polynucleotides are condensed to a size in the range of about 20 nm to about 50 nm, does not reasonably provide enablement for complexes of

polynucleotides and other condensing agents wherein the polynucleotides are condensed to a size in the range of about 20 nm to about 50 nm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Independent claim 72 requires that the aerosol particles must comprise polynucleotides condensed with a condensing agent, wherein the size of the condensed polynucleotides is from about 20 to about 50 nm. Guidance in the specification as to how to obtain these particles is limited to page 10, where it is disclosed that polycations can be used to achieve this degree of condensation. The only condensing agents other than a polycation that are disclosed in the specification are cationic lipids. However, the specification does not teach how to use cationic lipids to condense nucleic acids into the claimed size range. The art taught examples of complexes of cationic lipids and nucleic acids that were as small as 160 nm (see Rothenpieler et al (US2003/0124093, paragraph 48 at page 7), and liposomes comprising nucleic acids in the size range of 50-150 nm (see e.g. (Wheeler et al (US 5,976,567, column 16, lines 35-57, or Saravolac et al (J. Drug Targ. 7(6): 423-437, 2000) abstract, Table II at page 430, and Fig. 5 at page 432). Neither the specification nor the art of record teach how to condense nucleic acids to 20-50 nm without the use of polycations. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a

process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identity of condensing agents, other than polycations that can provide the required size particle is not a detail that can be omitted in the process of enabling the full breadth of the claims.

It is suggested that the claims should be amended to require a polycation condensing agent.

It should be noted that the prior art taught that polycations and nucleic acids generally formed charge-based complexes in the range of 20-80 nm (see Tang et al (Gene Therapy, 4: 823-832, 1997), abstract and Fig. 4 on page 832), and that the prior art also taught that polyplexes of lipids, polycations and nucleic acids were larger than this range. See for example Mack (Am. J. Med. Sci. 307(2): 138-143, 1992) and Huang (US Patent 6,008,202, issued 12/28/99). Mack shows that complexes of cationic lipids, nucleic acids, and polycations formed in the range of about 100 nm to 2800 nm, with most ranging from about 200-560 nm. See Fig. 4 on page 140. Huang looked at the size of 45 different complexes comprising different ratios of nucleic acids, lipids, and

polycations. All complexes were in the range of 170-3500 nm. See Fig. 20. However, although addition of a cationic lipid to a polycation-condensed nucleic acid results in a larger particle, there is no evidence to suggest that it results in decondensation of the nucleic acid. In other words, there is no evidence that polycation-condensed nucleic acids in polyplexes are larger than 20-80 nm. So, the claims are considered to be enabled for aerosol particles comprising nucleic acid/polycation/cationic lipid polyplexes wherein the nucleic acid is in the size range of 20-50 nm.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following rejections each cite the Schuster reference, US Patent 5,906,202, issued 5/25/99, which has an inventor in common with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the

reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Because Applicant has filed a terminal disclaimer over US Patent 5,906,202, the '202 patent will be disqualified as prior art if Applicant files an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104.

Claims 59, 60, 63, 66, 67, and 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99) in view of Scanlin et al (US Patent 5,948,681, issued 9/7/99), Tang et al (Gene Therapy, 4: 823-832, 1997), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Schuster taught a device and method of delivering a volume of aerosol to a target area of a lung. The method comprises measuring a volume of particle-free air inhaled into the lungs, drawing a measured volume of aerosol into the respiratory tract,

and inhaling an additional volume of particle-free air, insufficient to fill the upper region of the patient's respiratory tract. Each of these three inhalation volumes is controlled. See e.g. claim 3 at column 38. Schuster teaches the delivery of gene vectors in carriers by this method. See column 2, line 33; paragraph bridging columns 7 and 8; paragraph bridging columns 30 and 31, and claims 11-13. The method involves adjusting the size of aerosol particles during delivery. Schuster teaches using aerosol particle sizes from 1-10 microns in aerodynamic diameter, and the adjustment of particle size in order to target specific regions of lung. See item c of claim 1; column 12, lines 37, 38, and 47-49; column 20, lines 30-50; and paragraph bridging columns 20 and 21. Schuster also teaches adjusting inspiratory flow rate to 0.2 to 3 liters per second. See claim 14; and column 12, lines 34-36. Note that the instant specification at page 27, lines 17-19 states that the device of Schuster is useful for the instant method. Note also that the specification states in that same passage that the Schuster patent was commonly owned at the time of filing (see double patenting rejections below). Under 35 USC 103 (a) and (c), the Schuster patent is considered prior art because the instant Application was filed prior to 11/29/1999.

Schuster did not teach the use of a condensing agent or condensed nucleic acids in a size range of 20-50 nm, nor did Schuster explicitly distinguish between delivery to alveoli, central airways and upper airways.

Scanlin suggested transfection of lung cells in vivo by aerosol delivery of polycation condensed DNA. See detailed description paragraphs 40-44, 83, and 149-151.

Tang taught that cationic nucleic acid condensing agents, such as polylysine, polyethyleneimine, and fractured or intact polyamidoamine dendrimers, form toroidal particles on the order of about 20-80 nm when complexed with DNA plasmids, with the majority of particles being 43-67 nm. See abstract and Fig. 4 on page 832.

Radhakrishnan teaches that depth of penetration of aerosol particles into the respiratory tract is inversely related to the aerodynamic diameter of the particles, and discloses what size particles will reach various parts of the lung. See e.g. Fig. 3.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the delivery composition of Scanlin in the method of Schuster. One would have been motivated to do so because Scanlin suggests that polylysine/DNA complexes provide a high level of efficiency compared to other carriers. See Brief Description paragraph 15. It is evident from the teachings of Tang that polycations, including polylysine, generally condense plasmid DNAs to a size of 20-80 nm. Schuster teaches the entire range of aerosol particle sizes recited in the instant claims, and it was well-recognized in the prior art, in view of Radhakrishnan and Schuster, that different areas of the respiratory tract were targeted by different sized aerosol particles. It would have been obvious to adjust the size of aerosol particles to particular aerodynamic diameters in order to target various sites in the respiratory tract, because Debs suggests that this should be done. The size of the particles is clearly a result effective variable, the optimization of which is routine in the art particularly in view of Radhakrishnan who establishes the relationship between particle size and depth of penetration into the respiratory tract.

Furthermore, based on the teachings of Tang, it would have been obvious to substitute polyethylenimine, or other polycations such as dendrimers, for polylysine because these polycations all appear to be functional equivalents as DNA condensation/transfection agents. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99), Scanlin et al (US Patent 5,948,681, issued 9/7/99), Tang et al (Gene Therapy, 4: 823-832, 1997), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91) as applied to claims 59-60, 63, 66, 67, and 69-72 above, and further in view of Debs (US Patent 5,756,353, issued 5/26/98).

The teachings of Schuster, Scanlin, Tang, and Radhakrishnan are discussed above and render obvious methods of targeting an area of a patient's respiratory tract comprising aerosolizing a formulation comprising polynucleotides condensed to a size of 20-50 nm, adjusting the aerodynamic diameter of the particles based on the targeted

area of a patient's respiratory tract, and controlling the patient's inhaled volume of aerosolized formulation and aerosol-free air.

The combined references do not specifically provide motivation to deliver complexes to the alveoli.

Debs taught a method of targeting an area of a patient's respiratory tract by delivering to the patient an aerosol comprising condensed DNA. See abstract and column 11, lines 24-26. The size of the aerosol particles is adjusted based on the intended delivery site within the respiratory tract. A size range of from 0.5-5 microns is suggested for alveoli, and a size range of 4-12 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16.

It would have been obvious to one of ordinary skill in the art at the time of the invention to delivery condensed nucleic acids to the alveoli, and to adjust the aerosol particle size in the range of 1-3 microns because Debs suggests delivery of condensed nucleic acids to the alveoli, and teaches adjustment of aerosol particle size to a range overlapping that of the instant claims. Absent some evidence that the claimed range provides some unexpected benefit, it would have been routine for one of ordinary skill in the art to determine the particle size within the small range set forth by Debs.

Claims 63, 64, 68, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99), in view of Scanlin et al (US Patent 5,948,681, issued 9/7/99), Tang et al (Gene Therapy, 4: 832-

832, 1997), Radhakrishnan (US Patent 5,049,389, issued 9/17/91), and Chu et al (US Patent 6,030,834, issued 2/29/00).

The teachings of Schuster, Scanlin, Tang, and Radhakrishnan are discussed above and render obvious methods of targeting an area of a patient's respiratory tract comprising aerosolizing a formulation comprising polynucleotides condensed with polylysine or polyethylenimine to a size of 20-50 nm, adjusting the aerodynamic diameter of the particles based on the targeted area of a patient's respiratory tract, and controlling the patient's inhaled volume of aerosolized formulation and aerosol-free air.

The combined references do not teach the use of protamine sulfate, spermine, spermidine, or putrescine as a condensing agent.

Chu taught that polycationic condensing agents include polylysine, polyarginine, polyornithine, protamine, spermine, spermidine, and putrescine. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered putrescine to be equivalent to protamine, spermine, and spermidine as a nucleic acid condensing agent.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicants arguments filed 11/19/04 have been considered as they apply to the grounds of rejection set forth above, but are not persuasive.

Applicant asserts that the '202 patent is not prior art with respect to the present invention. This is incorrect for the reasons set forth above under Priority, i.e. the '202 patent does not support the instant claims to the extent that they are drawn to condensed nucleic acids of a size from about 20 to about 50 nanometers, or to the use of polycations or cationic lipids. Applicant has pointed to no place in the disclosure of '202 that supports these claim limitations. In the absence of such support, the effective priority date for the instant claims is that of the instant application.

In the paragraph bridging pages 5 and 6 of the response, Applicant argues that the cited art does not teach a condensed polynucleotide of 20-50 nanometers. This argument was persuasive with regard to the rejections in the previous Action, but is now moot in view of the Tang reference cited above.

At page 6, Applicant asserts that the cited art does not teach adjusting the aerodynamic diameter of the aerosolized particles based on the targeted area of the patient's lungs. This is incorrect. Schuster and Radhakrishnan teach this limitation as discussed above. The recited size of the condensed nucleic acids in the aerosol is accounted for by the Tang reference. Applicant also argues that the cited art fails to teach controlling the patient's inhaled volume of aerosolized formulation and the volume

of aerosol-free air. This is incorrect. Schuster teaches these limitations. See e.g. claim 3 at column 38.

Applicant also appears to argue at page 6 that the filing of a terminal disclaimer over the '202 patent renders it inapplicable as prior art. The filing of the terminal disclaimer overcomes the double patenting rejections of record. However, as discussed above, the terminal disclaimer is insufficient to disqualify Schuster as a prior art reference. An oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104 is also required. Alternatively, appropriate oaths under 37 CFR 1.131 or 1.132 as discussed above could disqualify Schuster.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Richard Schnizer, Ph.D.